General

Guideline Title

BCSH/BSBMT guideline: diagnosis and management of veno-occlusive disease (sinusoidal obstruction syndrome) following haematopoietic stem cell transplantation.

Bibliographic Source(s)

Dignan FL, Wynn RF, Hadzic N, Karani J, Quaglia A, Pagliuca A, Veys P, Potter MN. BCSH/BSBMT guideline: diagnosis and management of veno-occlusive disease (sinusoidal obstruction syndrome) following haematopoietic stem cell transplantation. Br J Haematol. 2013 Nov;163(4):444-57. [99 references] PubMed

Guideline Status

This is the current release of the guideline.

Recommendations

Major Recommendations

Definitions for the quality of the evidence (A–C) and strength of recommendations (strong [grade 1], weak [grade 2]) are given at the end of the "Major Recommendations" field.

Diagnosis

Diagnostic Techniques

- It is recommended that the diagnosis of veno-occlusive disease (VOD) (sinusoidal obstruction syndrome) be based primarily on established clinical criteria (modified Seattle or Baltimore criteria) (1A).
- Ultrasound imaging may be helpful in the exclusion of other disorders in patients with suspected VOD (sinusoidal obstruction syndrome) (1C).
- It is recommended that liver biopsy be reserved for patients in whom the diagnosis of VOD (sinusoidal obstruction syndrome) is unclear and there is a need to exclude other diagnoses (1C).
- It is recommended that liver biopsies are undertaken using the transjugular approach in order to reduce the risks associated with the procedure (1C).
- It is suggested that the role of plasminogen activator inhibitor-1 levels remains an area for further research but that these levels do not form part of the routine diagnostic work-up for VOD (sinusoidal obstruction syndrome) at present (2C).

Prevention of VOD

- It is recommended that patients are assessed for risk factors for VOD (sinusoidal obstruction syndrome) and that these risk factors are

addressed prior to haematopoietic stem cell transplantation (1A).

- Defibrotide is recommended at a dose of 6.25 milligrams/kg intravenously 4 times daily for the prevention of VOD (sinusoidal obstruction syndrome) in children undergoing allogeneic stem cell transplantation with the following risk factors: pre-existing hepatic disease, second myeloablative transplant, allogeneic transplant for leukaemia beyond second relapse, conditioning with busulfan containing regimens, prior treatment with gemtuzumab ozogamicin, diagnosis of primary haemophagocytic lymphohistiocytosis, adrenoleukodystrophy or osteopetrosis (1A).
- Defibrotide is suggested at a dose of 6.25 milligrams/kg intravenously 4 times daily for the prevention of VOD (sinusoidal obstruction syndrome) in adults undergoing allogeneic stem cell transplantation with the following risk factors: pre-existing hepatic disease, second myeloablative transplant, allogeneic transplant for leukaemia beyond second relapse, conditioning with busulfan containing regimens, prior treatment with gemtuzumab ozogamicin, diagnosis of primary haemophagocytic lymphohistiocytosis, adrenoleukodystrophy or osteopetrosis (2B).
- Prostaglandin E1 is not recommended in the prophylaxis of VOD (sinusoidal obstruction syndrome) due to lack of efficacy and toxicity (1B).
- Pentoxifylline is not recommended in the prophylaxis of VOD (sinusoidal obstruction syndrome) due to lack of efficacy (1A).
- Ursodeoxycholic acid is suggested for use in the prophylaxis of VOD (sinusoidal obstruction syndrome) (2C).
- Heparin (unfractionated and low molecular weight) is not suggested for use in the prophylaxis of VOD (sinusoidal obstruction syndrome) due to the risk of increased toxicity (2B).
- Anti-thrombin is not suggested for the prophylaxis of VOD (sinusoidal obstruction syndrome) due to lack of efficacy (2B).

Treatment of VOD

- Defibrotide is recommended in the treatment of VOD (sinusoidal obstruction syndrome) in adults and children (1B).
- Tissue plasminogen activator (TPA) is not recommended for use in the treatment of VOD (sinusoidal obstruction syndrome) due to the associated risk of haemorrhage (1B).
- N-acetylcysteine is not routinely recommended for use in the treatment of VOD due to lack of efficacy (1A).
- Methylprednisolone may be considered for use in the treatment of VOD with the appropriate caveats of caution regarding infection (2C).
- Judicious clinical care particularly in the management of fluid balance is recommended in the management of VOD (sinusoidal obstruction syndrome) (1C).
- Early discussion with critical care specialists and a specialist hepatology unit is recommended in the management of VOD (sinusoidal obstruction syndrome) and other treatment options including transjugular intrahepatic portosystemic shunt (TIPS) or hepatic transplantation may be considered (1C).

Definitions:

Quality of Evidence

The quality of evidence is graded as high (A), moderate (B) or low (C). To put this in context it is useful to consider the uncertainty of knowledge and whether further research could change what is known or is certain.

(A) High Further research is very unlikely to change confidence in the estimate of effect. Current evidence derived from randomised clinical trials without important limitations.

(B) Moderate Further research may well have an important impact on confidence in the estimate of effect and may change the estimate. Current evidence derived from randomised clinical trials with important limitations (e.g., inconsistent results, imprecision – wide confidence intervals or methodological flaws – e.g., lack of blinding, large losses to follow up, failure to adhere to intention to treat analysis), or very strong evidence from observational studies or case series (e.g., large or very large and consistent estimates of the magnitude of a treatment effect or demonstration of a dose-response gradient).

(C) Low Further research is likely to have an important impact on confidence in the estimate of effect and is likely to change the estimate. Current evidence from observational studies, case series or just opinion.

Strength of Recommendations

Strong (grade 1): Strong recommendations (grade 1) are made when there is confidence that the benefits do or do not outweigh harm and burden. Grade 1 recommendations can be applied uniformly to most patients. Regard as 'recommend'.

Weak (grade 2): Where the magnitude of benefit or not is less certain a weaker grade 2 recommendation is made. Grade 2 recommendations require judicious application to individual patients. Regard as 'suggest'.

Clinical Algorithm(s)

None provided

Scope

Disease/Condition(s)

Veno-occlusive disease (sinusoidal obstruction syndrome) following haematopoietic stem cell transplantation

Guideline Category

Diagnosis

Evaluation

Management

Prevention

Risk Assessment

Treatment

Clinical Specialty

Gastroenterology

Hematology

Internal Medicine

Pediatrics

Preventive Medicine

Surgery

Intended Users

Advanced Practice Nurses

Physician Assistants

Physicians

Guideline Objective(s)

To provide recommendations for the diagnosis and management of veno-occlusive disease of the liver following haematopoietic stem cell transplantation

Target Population

Children and adults undergoing haematopoietic stem cell transplantation

Interventions and Practices Considered

Diagnosis/Risk Assessment

1. Use of established clinical criteria (modified Seattle or Baltimore criteria) for diagnosis
2. Ultrasound
3. Liver biopsy
4. Assessment for risk factors

Prevention/Treatment/Management

1. Defibrotide
2. Ursodeoxycholic acid
3. Methylprednisolone
4. Judicious clinical (fluid balance)
5. Discussion with critical care specialists
6. Transjugular intrahepatic portosystemic shunt (TIPS)
7. Hepatic transplantation

Note: The following are not recommended: prostaglandin E1, pentoxifylline, heparin, and anti-thrombin for prophylaxis of veno-occlusive disease (VOD), and tissue plasminogen activator (TPA), N-acetylcysteine for treatment of VOD.

Major Outcomes Considered

- Clinical, histopathologic, and imaging features of veno-occlusive disease (VOD)
- Risk factors associated with VOD
- Treatment-related toxicity and adverse events
- Efficacy of VOD prevention (e.g., measured by incidence of VOD, mortality)
- Efficacy of VOD treatment (e.g., measured by resolution of VOD, complete response rate, survival rate)

Methodology

Methods Used to Collect/Select the Evidence

Searches of Electronic Databases

Description of Methods Used to Collect/Select the Evidence

The production of these guidelines involved establishment of a working group comprising experts in the field of allogeneic transplantation followed by literature review to 15/2/2013. Medline was searched systematically for publications in English using the following key words: veno-occlusive disease and sinusoidal obstruction syndrome. The reports of major conferences were also reviewed using the same keywords.

Number of Source Documents

Not stated

Methods Used to Assess the Quality and Strength of the Evidence

Weighting According to a Rating Scheme (Scheme Given)

Rating Scheme for the Strength of the Evidence

Quality of Evidence

The quality of evidence is graded as high (A), moderate (B) or low (C). To put this in context it is useful to consider the uncertainty of knowledge and whether further research could change what is known or is certain.

(A) High Further research is very unlikely to change confidence in the estimate of effect. Current evidence derived from randomised clinical trials without important limitations.

(B) Moderate Further research may well have an important impact on confidence in the estimate of effect and may change the estimate. Current evidence derived from randomised clinical trials with important limitations (e.g., inconsistent results, imprecision – wide confidence intervals or methodological flaws – e.g., lack of blinding, large losses to follow up, failure to adhere to intention to treat analysis), or very strong evidence from observational studies or case series (e.g., large or very large and consistent estimates of the magnitude of a treatment effect or demonstration of a dose-response gradient).

(C) Low Further research is likely to have an important impact on confidence in the estimate of effect and is likely to change the estimate. Current evidence from observational studies, case series, or just opinion.

Methods Used to Analyze the Evidence

Review of Published Meta-Analyses

Systematic Review

Description of the Methods Used to Analyze the Evidence

The Grading of Recommendations Assessment, Development, and Evaluation (GRADE) nomenclature was used to evaluate levels of evidence (see the "Rating Scheme for the Strength of the Evidence" field).

Methods Used to Formulate the Recommendations

Expert Consensus

Description of Methods Used to Formulate the Recommendations

A joint working group established by the Haemato-oncology subgroup of the British Committee for Standards in Haematology (BCSH) and the British Society for Bone Marrow Transplantation (BSBMT) has reviewed the available literature and made recommendations for the diagnosis and management of veno-occlusive disease of the liver following haematopoietic stem cell transplantation.

The production of these guidelines involved the following steps:

- Development of key recommendations based on randomised, controlled trial evidence. Due to the paucity of randomised studies some recommendations are based on literature review and a consensus of expert opinion.
- The Grading of Recommendations Assessment, Development, and Evaluation (GRADE) nomenclature was used to assess the strength of recommendations. The GRADE criteria are specified in the BCSH guideline pack and the GRADE working group website. See the "Rating Scheme for the Strength of the Recommendations" field. Further information is available from the following websites:
  - http://www.bcshguidelines.com/BCSH_PROCESS/42_EVIDENCE_LEVELS_AND_GRADES_OF_RECOMMENDATION.html (accessed 28/6/2013)
  - http://www.gradeworkinggroup.org/index.htm (accessed 28/6/2013)

Rating Scheme for the Strength of the Recommendations

Strength of Recommendations

Strong (grade 1): Strong recommendations (grade 1) are made when there is confidence that the benefits do or do not outweigh harm and burden.

Grade 1 recommendations can be applied uniformly to most patients. Regard as 'recommend'.

Weak (grade 2): Where the magnitude of benefit or not is less certain a weaker grade 2 recommendation is made. Grade 2 recommendations require judicious application to individual patients. Regard as 'suggest'.

Cost Analysis

A formal cost analysis was not performed and published cost analyses were not reviewed.

Method of Guideline Validation

External Peer Review

Internal Peer Review

Description of Method of Guideline Validation

The production of these guidelines involved the following steps:

- Review by the British Committee for Standards in Haematology (BCSH) committees, British Society of Blood and Marrow Transplantation (BSBMT) executive committee, and the UK Paediatric Bone Marrow Transplant Group
- Review by sounding board of the British Society for Haematology (BSH) and allogeneic transplant centres in the UK

Evidence Supporting the Recommendations

Type of Evidence Supporting the Recommendations

The type of supporting evidence is identified and graded for each recommendation (see the "Major Recommendations" field).

Benefits/Harms of Implementing the Guideline Recommendations

Potential Benefits

Appropriate diagnosis and management of veno-occlusive disease (sinusoidal obstruction syndrome) following haematopoietic stem cell transplantation

Potential Harms

In a single arm phase II study of defibrotide, the main toxicities were haemorrhage in 18% and hypotension in 4% of patients with 2% of patients experiencing life-threatening haemorrhage.

Contraindications

Contraindications

- Prostaglandin E1 is not recommended in the prophylaxis of veno-occlusive disease (VOD) (sinusoidal obstruction syndrome) due to lack of efficacy and toxicity.
- Tissue plasminogen activator (TPA) is not recommended for use in the treatment of VOD (sinusoidal obstruction syndrome) due to the

associated risk of haemorrhage.

Qualifying Statements

Qualifying Statements

- While the advice and information in these guidelines is believed to be true and accurate at the time of going to press, neither the authors, the British Society for Haematology, nor the British Society of Blood and Marrow Transplantation nor the publishers accept any legal responsibility for the content of these guidelines.
- Defibrotide is an unlicensed drug and clinicians using this agent should be aware that its use does not have approval of regulatory authorities. The role of this agent is discussed in these guidelines for prophylaxis and treatment of veno-occlusive disease (sinusoidal obstruction syndrome) as there are no similar licensed agents available.
- The use of defibrotide in adults undergoing haematopoietic stem cell transplantation would be at the discretion of the treating physician as it is an unlicensed drug and, at present, the data available primarily relates to its use in children.

Implementation of the Guideline

Description of Implementation Strategy

An implementation strategy was not provided.

Institute of Medicine (IOM) National Healthcare Quality Report Categories

IOM Care Need

Getting Better

Living with Illness

Staying Healthy

IOM Domain

Effectiveness

Patient-centeredness

Identifying Information and Availability

Bibliographic Source(s)

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Adaptation

Not applicable: The guideline was not adapted from another source.

Date Released

2013 Nov

Guideline Developer(s)

British Society for Haematology Guidelines - Professional Association

British Society of Blood and Marrow Transplantation - Professional Association

Source(s) of Funding

British Committee for Standards in Haematology

Guideline Committee

Haemato-oncology Task Force of the British Committee for Standards in Haematology and the British Society for Blood and Marrow Transplantation

Composition of Group That Authored the Guideline

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Financial Disclosures/Conflicts of Interest

FLD, JK, AQ, NH, and PV have no conflicts of interest to declare. MNP, RFW, and AP have participated in an advisory board for Gentium. AP has received speaker's fees from Gentium.

Guideline Status

This is the current release of the guideline.

Guideline Availability

Electronic copies: Available from the British Journal of Haematology Web site .

Print copies: Available from the British Committee for Standards in Haematology; Email: bcsh@b-s-h.org.uk.

Availability of Companion Documents

None available

Patient Resources

None available

NGC Status

This NGC summary was completed by ECRI Institute on October 18, 2013.

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